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Danazol for Paroxysmal Nocturnal Hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal stem-cell disorder in which blood cells lack complement inhibiting membrane proteins, and become susceptible to complement-mediated injury, leading to chronic intravascular hemolysis and pancytopenia. Glucocorticoids have been a mainstay of therapy. For patients refractory to glucocorticoids and requiring blood transfusions, an alternative therapy is needed. We studied danazol therapy in 5 patients refractory to other treatments. Four of the 5 benefited, showing rise in hematocrit and eventual cessation of transfusion requirements. Remissions lasted ≥2 years in 3 and 10 years in 1 patient. Danazol was well-tolerated without serious side effects. Danazol appears to be a good alternative treatment in PNH. Am. J. Hematol. 54:149–154, 1997 © 1997 Wiley-Liss, Inc.

Key words: Danazol; PNH; androgen therapy

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal disorder of hematopoietic stem cells. The blood cells in PNH lack GPI-anchored membrane proteins, including those that protect against complement-mediated homologous lysis. This defect leads to chronic intravascular hemolysis requiring blood transfusions, neutropenia, a factor predisposing to infections, and thrombocytopenia, as well as thrombotic complications [1–5].

Treatment of PNH consists mainly of supportive measures such as packed cell transfusions for anemia, antibiotic treatment for infections, and antithrombotic therapy for thrombosis [2,6]. Glucocorticoids (GC) have been most often used. They improve the hematologic picture in most, but high dosage and long-term treatment is required, resulting in serious side effects [6,7]. Androgens were also reported useful in PNH; they are thought to stimulate erythropoiesis and to retard hemolysis through inhibition of complement activation [6,8]. Androgen therapy has been recommended in PNH associated with aplastic or hypoplastic bone marrow [6]. However, androgens are not well-tolerated in women and their use is not widely accepted. Other measures have included vitamin E to inhibit peroxidation of membranes [9], and high-dose recombinant human erythropoietin [10]. Allogeneic bone-marrow transplant has been employed successfully in selected cases of PNH [11,12] but carries high morbidity and is applicable only to those having HLA-matched donors. Long-term spontaneous remission occurs in certain cases, which must be taken into consideration when potentially dangerous treatments such as bone-marrow transplant are contemplated [13].

Danazol (Danocrine™) is an attenuated androgen initially formulated to treat endometriosis [14]. It was subsequently found useful in patients with hereditary angioedema [15]. Subsequently, application of danazol was extended to autoimmune thrombocytopenia [16], hemolytic anemia [17], and other hematologic and autoimmune disorders [18]. We report here our clinical experience with danazol in the treatment of PNH [19].

CASE STUDIES

Case 1

A 50-year-old white woman developed anemia and dark urine in 1978, shortly before immigrating from Cuba

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in 1979. She was treated with prednisone and oral iron but needed frequent transfusions. Laboratory investigation revealed negative Coomb's test, positive Ham's and sugar water tests, and positive urine hemosiderin. She was seen for the first time at the University of Miami Hospital and Clinics (UMHC) in July 1980, when her hemoglobin (Hb) was 5.7 g/dl, hematocrit (Hct) was 18%, reticulocytes were 25%, WBC was 6,200/mm^3, platelet count (plt) was 440,000/mm^3, LDH was 2,625 U/l, total bilirubin was 1.8 mg/dl, and direct bilirubin was 0.2 mg/dl. She was initially treated with prednisone 20–30 mg/day, vitamin E 800 IU/day, folic acid, oral iron, Halotestin, and Delatestryl. The prednisone was reduced to 30 mg every other day because of weight gain and Cushing's syndrome. For 2 years she required transfusions of 3–4 units of packed cells every 2 months. In May 1982, danazol 800 mg/day was added to her regimen. A single transfusion was needed in October 1982, and again in January and March 1983. Her blood counts gradually improved, with less frequent transfusions. Since September 1983, her Hct remained 28–33% without further transfusion, with reticulocytes 7–18%. In early 1984, prednisone and danazol were stopped when her Hct fell to 25% with dark urine. Both drugs were resumed and anemia improved again. In 1985, danazol was reduced to 400 mg/day, then later to 200 mg/day, while her Hct held at 30–33%. She discontinued danazol and did not return for follow-up until 1995. She remains in hematologic remission without danazol therapy.

Case 2

A 17-year-old girl from South America was referred to UMHC for evaluation of anemia, dark urine, and unconjugated hyperbilirubinemia of 5 months duration in November 1972. Her Hb was 5.7 g/dl, Hct was 18%, and reticulocytes were 25%. Coomb's test was negative, total bilirubin was 3.2 mg/dl, with direct bilirubin of 1.1 mg/dl. Ham's test, sugar water test, and urine hemosiderin were positive. She was initially treated with prednisone, oral iron, folic acid, and periodic transfusions of packed cells. Vitamin E and androgens (Delatestryl and Halotestin) were also tried, as was vincristine. In August 1974 she developed fever, abdominal pain, and partial bowel obstruction. Abdominal x-ray revealed dilated small bowel loops with thickened mucosa, consistent with mesenteric vein thrombosis. She was treated with IV fluids, antibiotics, and NG suction, with a gradual recovery. Aspirin was added to her regimen. She was married and became pregnant in early 1976, and delivered a healthy boy. During her pregnancy she did well without Tx requirements, but following delivery her anemia worsened. Her dosage of prednisone in following years ranged from 60 mg/day during periods of severe anemia, to 10–50 mg every other day during stable phases. In February 1983 she was admitted with abdominal pain and fever, and was found to have a gallstone. She was treated with IV antibiotics with gradual improvement. Her Hb was 7.9 g/dl, Hct was 23.5%, WBC was 5,100/mm^3, plt was 53,000/mm^3, and reticulocytes were 7.8%. Danazol 400 mg/day was added, then increased to 800 mg/day, and prednisone was discontinued. A short trial of Delatestryl was administered. Transfusion of packed cells was needed in April, May, and July of 1983, but in August of 1983 and through 1984–1985 she needed no Tx and her Hb and Hct were stable at 9–12 g/dl and 27–34%, respectively, with reticulocytes 7–20%. She tolerated danazol fairly well, though complained of weight gain and acne. Several attempts to reduce or stop danazol were associated with hematologic deterioration, and resumption of danazol improved blood counts; her Hct stayed around 30% and her platelets ranged from 90,000–150,000/mm^3 for 3 years with maintenance danazol therapy. We lost her to follow-up.

Case 3

A 40-year-old white male sought urologic consultation in May 1989 because of red urine. Urologic workup was negative for hematuria; he was found to have hemoglobinuria and hemolytic anemia. He also complained of fatigue and poor appetite. His Hb was 4 g/dl, reticulocytes were 6.1%, LDH was 2,032 U/l, alkaline phosphatase was 786 U/l, and total bilirubin was 5.3 mg/dl. ANA and RF were negative. He was placed on prednisone and danazol (800 mg/day). He experienced side effects (weight gain, nervousness), and required blood Tx. Danazol was discontinued and prenisone was reduced from 80 to 30 mg/day. In June 1989, his Hb was 4.5 g/dl, Hct was 16%, plt was 18.000/mm^3, and haptoglobin was <5 mg/dl, with positive Ham's test and positive urine hemosiderin. He was placed on danazol 600 mg/day, folic acid 2 mg/day, and ferrous sulfate 50 mg/day, and prednisone was discontinued. He responded well, with Hct maintained at 30% with no further Tx required. Reduction of dosage of danazol was associated with falling Hct. By February 1990 he was in partial hematologic remission, with Hg 11 g/dl, and Hct 33%; danazol was reduced to 400 mg/day at this time. He received no further Tx after June 1989, and experienced no serious side effects. In December 1992 he was still clinically well, with Hg 10.7 g/dl, Hct 32%, and plt 148,000/mm^3. Dosage was reduced to 200 mg every other day. In December 1993 danazol was reduced to 200 mg twice weekly, and his counts remained stable. In February 1994 his counts were as follows: Hg 12.7 g/dl, Hct 38%, reticulocytes 3.6%, and plt 133,000/mm^3. For the last 6 years he has required no further Tx, and has been working full-time.

Case 4

This 46-year-old white man developed weakness and dark urine in the morning, dating from April 1984. Blood counts showed Hg 7.6 g/dl, Hct 22%, WBC 4,900/mm^3,

and plt 60,000/mm^3. He was treated with prednisone, oral iron, and folic acid, and he required Tx. When we saw him at UMHC in July 1984, his Hg was 9.2 g/dl, Hct was 26.8%, WBC was 2,000/mm^3, plt was 78,000/mm^3, and reticulocytes were 4.5%. Ham's test, sugar water test, and urine hemosiderin were positive. Coomb's test was negative. Total bilirubin was 1.4 mg/dl, with direct bilirubin of 0.2 mg/dl. Danazol 600 mg/day was added, and sporadic injections of Delatestryl were given in the early course of treatment preceding danazol therapy. High-dose prednisone was given initially, then tapered off and stopped completely in December 1984. In May 1985, his blood counts showed Hb 12.6 g/dl, Hct 37.7%, WBC 5,700/mm^3, plt 274,000/mm^3, and reticulocytes 8.4%. Throughout 1985–1986 he was maintained on danazol 600 mg/day, folic acid, and oral iron. His Hct remained around 34%. He experienced occasional dark urine. He expired from pneumonia while PNH had been in partial remission for more than 2 years.

Case 5

A 64-year-old retired plumber developed progressive weakness, and dyspnea on exertion. He had a long history of hypertension, atherosclerotic coronary heart disease, and congestive heart failure. Hematologic evaluation revealed anemia with Hb 7.0 gm/dl, Hct 19%, reticulocytes 8%, MCV 88 fl, WBC 8,400/mm^3, and plt 267,000/mm^3. Further study showed evidence of hemolysis with low haptoglobulin, high LDH, and positive Ham's test. Bone marrow showed erythroid hyperplasia without suggestion of leukemia or lymphoma. He was initially treated with prednisone 10–20 mg/day, and danazol 600–800 mg/day. He continued to require frequent blood transfusions, every 2–4 weeks, for a period of 5 months, and he expired from pneumonia and congestive heart failure. Autopsy revealed bilateral bronchopneumonia, coronary atherosclerosis with myocardial hypertrophy, congestion of lungs, chronic persistent hepatitis, and splenomegaly with hemosiderosis. Bone marrow revealed reactive hyperplasia without evidence of neoplasm.

MATERIALS AND METHODS

The above 5 patients with PNH were studied. All had documented PNH with positive Ham's test and clinical and laboratory parameters of chronic intravascular hemolysis. Their duration of PNH ranged from 2 months to 11 years prior to initiation of danazol therapy. All had been treated previously with prednisone, folic acid, and iron. All except case 4 had also been treated with Halotestin or Delatestryl. High-dose vitamin E had been tried on cases 1 and 2, and aspirin had been given to prevent thromboembolic complications. All patients had failed on glucocorticoids and other measures, requiring blood transfusions. Pertinent data on these patients are summarized in Table I.

Danazol 400–800 mg/day was added to the previous medications. In cases 1, 2, and 4, a short course of high-dose prednisone and Delatestryl was given initially. Blood counts, chemistries (total and direct bilirubin, LDH, etc.), and transfusion requirements were monitored before and during danazol treatment. As hematologic parameters improved, the dosage of prednisone was gradually reduced, and was eventually discontinued in all patients.

RESULTS

All patients in this series had previously failed on glucocorticoids and required transfusions (Tx) despite multiple medical therapies. In 4 of the 5, danazol therapy was associated with increased hematocrit and elimination of transfusion requirements (see Table I). The hematologic improvement was sustained for 2 years or more in all 4 responders, and for 10 years in case 1. In case 1, danazol induced remission with cessation of Tx requirement, but when danazol was discontinued at 18 months of treatment, relapse occurred. Retreatment with danazol again induced remission. Danazol was discontinued after a total of 3 years of treatment, and the patient remained in remission for 10 years without danazol. In cases 2 and 3, continuous maintenance therapy with danazol was required to hold their hematocrits at approximately 30%; efforts to discontinue danazol were associated with relapse in these two cases. Case 4 was treated with danazol 600 mg/day for more than 2 years to maintain partial hematologic remission.

Response to danazol was evident in 3 months in cases 3 and 4, both of whom had had a relatively short prior duration of disease (2–3 months). Cases 1 and 2, having longer prior duration of PNH, required 10 and 7 months, respectively, until they no longer required blood transfusion.

All 4 responders showed reticulocytosis during remission, and hemoglobinuria persisted but became less frequent. Thrombocytopenia, if present, improved significantly with danazol therapy. No hematologic improvement was seen in case 5 who, despite 5 months of danazol therapy, continued to require blood transfusion and eventually expired with pneumonia. Case 2 had previously experienced thromboembolic complications, but has been free of thrombosis since danazol therapy. None of the responders experienced thromboembolic episodes during danazol therapy.

Danazol was well-tolerated in all patients. Case 2 developed acne, but this condition seemed improved by addition of tamoxifen; this patient also complained of weight gain. Case 3 also developed bothersome weight gain while on danazol. See Table I for summary and Case Reports for details.

TABLE I. Clinical Data on 5 PNH Patients on Danazol Therapy

Case no. (age/sex)	Duration of PNH	Previous Rx	Danazol Therapy: Hematocrit (%) before/after	Reticulocyte count (%) before/after	WBC (×1,000/μl) before/after	Platelet count (×1,000/μl) before/after	Packed cell transfusion before/after	Comments
1 (50/F)	4 years	Glucocorticoids, Halotestin	22/32	15/20	6.2/7.7	340/414	every (q) 2 months/ none after 10 month's Rx	Remission for 10 years; danazol discontinued (d/c) after 3 years Rx
2 (31/F)	11 years	Glucocorticoids, Halotestin, Delatestryl,	21/33	10/12	3.0/5.0	61/100	q 1–3 months/ none after 7 month's Rx	Remission >3 years maintained with danazol
3 (42/M)	2 months	Glucocorticoids, Halotestin	16/30	6.1/3.5	4.0/4.9	18/133	1 Tx/none	Remission >6 years maintained with danazol
4 (46/M)	3 months	Glucocorticoids	22/37	4.5/5.7	4.9/5.7	60/274	q 3 weeks/ none after 3 month's Rx	Remission >2 years maintained with danazol (died of pneumonia)
5 (64/M)	6 months	Glucocorticoids, Halotestin	19/22	8/6	8.4/10.5	267/476	q 2–4 weeks/q 2–4 weeks	Nonresponder (died of pneumonia)

DISCUSSION

Use of androgens in the treatment of PNH has been advocated since Hartmann et al. [8] used fluoxymesterone in the treatment of 6 patients with PNH, 5 of whom showed significant improvement. They suggested that the benefit of androgen owed more to reduction of hemolysis than to stimulation of erythropoiesis.

It has been recommended that conventional androgen therapy be indicated in PNH associated with aplastic or hypoplastic bone marrow [6]. There has been some concern about the long-term safety of androgens, since anecdotal case reports on hepatocellular carcinoma [20] and peliosis hepatitis [21] associated with danazol therapy have been described. In each case, these effects could be coincidental rather than a result of danazol therapy. It has also been suggested that conventional androgen therapy may predispose to hepatic vein thrombosis [6]; however, a long-term study failed to document this complication [22]. None of these side effects was observed in this study.

In our responders, reticulocytosis before and during danazol therapy was comparable, and unconjugated hyperbilirubinemia and LDH tended to be decreased during remission when transfusion was not needed. Thus, the benefit of danazol appears to be attributable to reduced hemolysis rather than enhanced erythropoiesis, tending to confirm the report of Hartmann et al. [8]. None of our patients had hypoplastic or aplastic bone marrow.

Spontaneous remission can occur in PNH with a reported rate of 15% [13]. It may be argued that spontaneous remission could account for the benefits observed in our study, especially in case 1, in whom remission lasted for 10 years without maintenance therapy. However, this patient relapsed when danazol was discontinued during the early phase of remission, requiring reinstitution of danazol. The other 2 responders repeatedly relapsed upon withdrawal of the drug, and required maintenance therapy to keep stable hematocrits. These observations make it unlikely that spontaneous remission could account for the favorable results obtained in this study with danazol.

Whether danazol is more effective than other androgens in the treatment of PNH cannot be answered from this small study, though most of our patients had previously failed to respond to sporadic treatment with Halotestin or Delatestryl. Improvement in thrombocytopenia in all responders further suggests a unique action of danazol. Lack of venovascular occlusive complications in our study suggests another advantage of danazol over other androgens. Danazol has been shown to increase fibrinolytic activity, providing protection against thromboem-

bolic events [23]. Murakawa et al. [24] reported therapeutic benefits of danazol in 2 patients with PNH, substantiating our initial observations [19]. Danazol has been used with success in autoimmune hematologic diseases, hemolytic anemias [16–18], lupus-associated thrombocytopenia [25], and refractory pruritus [26].

The mechanisms of danazol therapy in hematologic disorders remain speculative. It would be of interest to study the effect of danazol therapy on CD55 or CD59 expression, since both are GPI-anchored and deficient in PNH. We did not have the opportunity to monitor CD59 before and after danazol therapy; however, 3 patients with PNH who were on danazol were evaluated and found to have only 10% or less of CD59 expression compared to controls [27]. We have observed that the red cells of patients on danazol become resistant to osmotic lysis [28], suggesting that danazol stabilizes the plasma membrane, and we have demonstrated by direct assay the accumulation of danazol in the membranes of RBC and platelets of patients on danazol [29]. It was also shown that danazol-treated platelets acquired resistance to complement-mediated lysis [29], consistent with danazol's protection of blood cells in PNH. Danazol was shown to modulate Fc receptor expression in monocytes [30] and to alter T-cell subsets in patients with ITP [31], in evidence of immunomodulatory actions of danazol. Accordingly, we suggest that the direct alteration of plasma membranes by danazol in PNH might be the major mode of benefit of danazol.

In summary, in our experience with this small group of patients, danazol appears useful in the management of PNH. Anemia and thrombocytopenia improved, and transfusion was no longer required in 4 of the 5 patients who responded. Danazol may offer the additional benefit of reducing the thrombotic complications often associated with PNH. It is well-tolerated and no serious side effects were observed. Further studies are needed to better define optimum treatment, safety, and the mechanism of action of danazol in a larger number of PNH patients.

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